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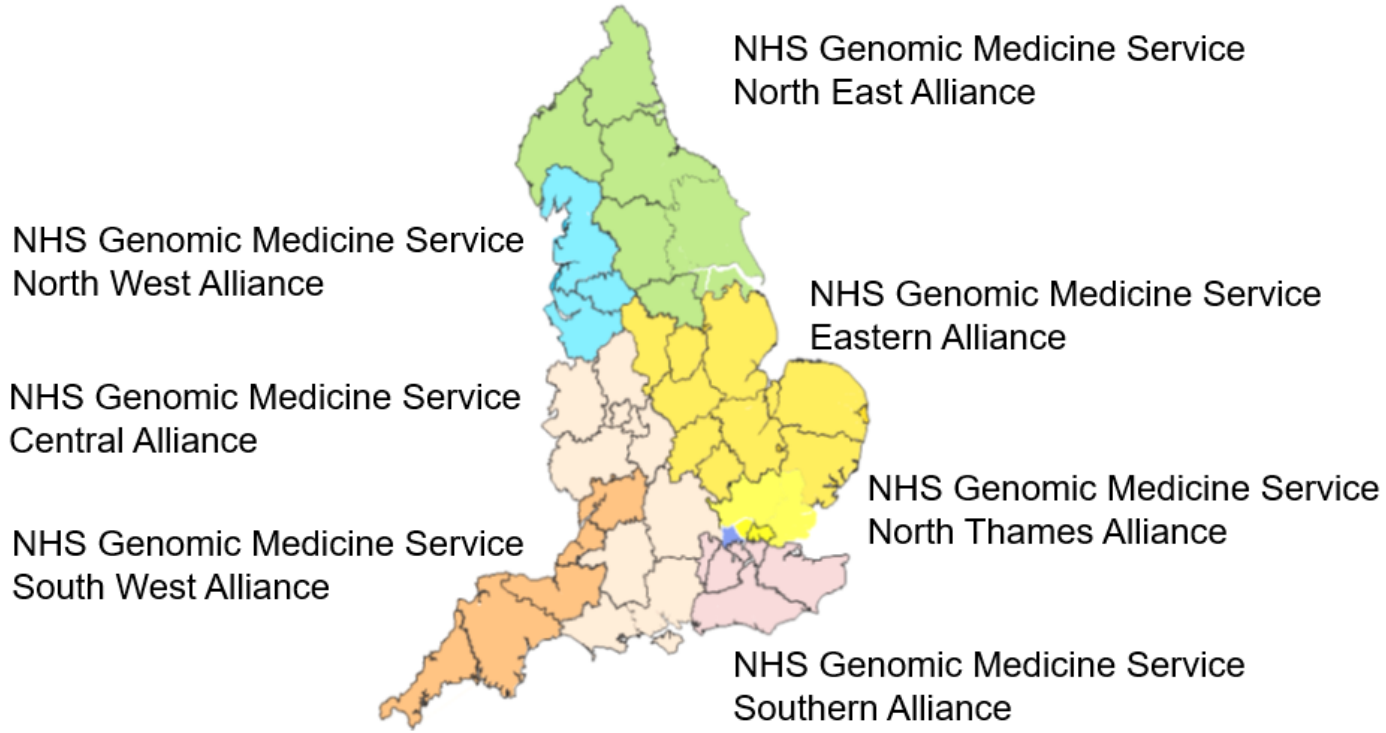
Genomics and Pharmacy and AMS

Dr Hayley Wickens

Consultant Pharmacist Genomic Medicine

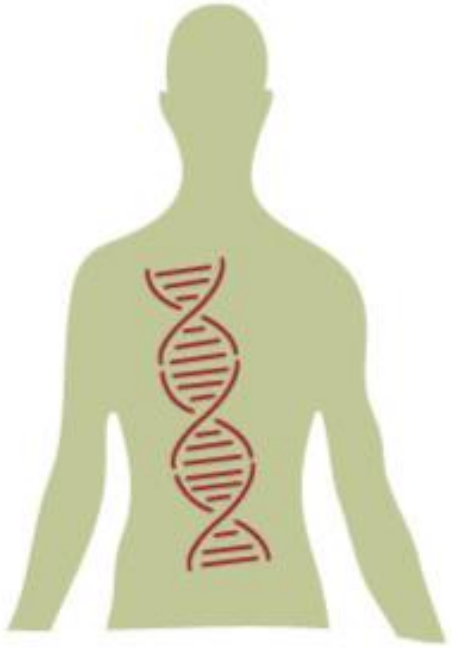
NHS Genomic Medicine Service

- **Regional infrastructures (NHS GMS Alliances)** to support the systematic embedding of genomic medicine
  - National co-ordination and oversight: Genomics Unit in NHSE/I
  - **Specialist pharmacist** and **chief pharmacist** in each GMSA



To personalise treatment and surveillance we can use genomic information...

from a person



- To sub-classify their disease
- To assess their susceptibility
- To predict their response to drugs
- To choose the best treatment

from a person's cancer

- To make a prognosis
- To target therapy to its genomic profile

from an infective organism

- To diagnose the type of infection
- To choose appropriate treatment
- To track epidemics

Drug treatment stratification using genomics

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Clinical diagnosis
HIV/AIDS
Drug (Abacavir) is known to be benefical

Approximately 20% of all new prescriptions in UK primary care have an actionable drug-gene interaction (Youssef et al 2021)

https://bpspubs.onlinelibrary.wiley.com/doi/pdf/10.1111/bcp.14704

Abacavir (not toxic) (3)	Abacavir (is toxic) (1)

Example of genomics in AMR testing: TB

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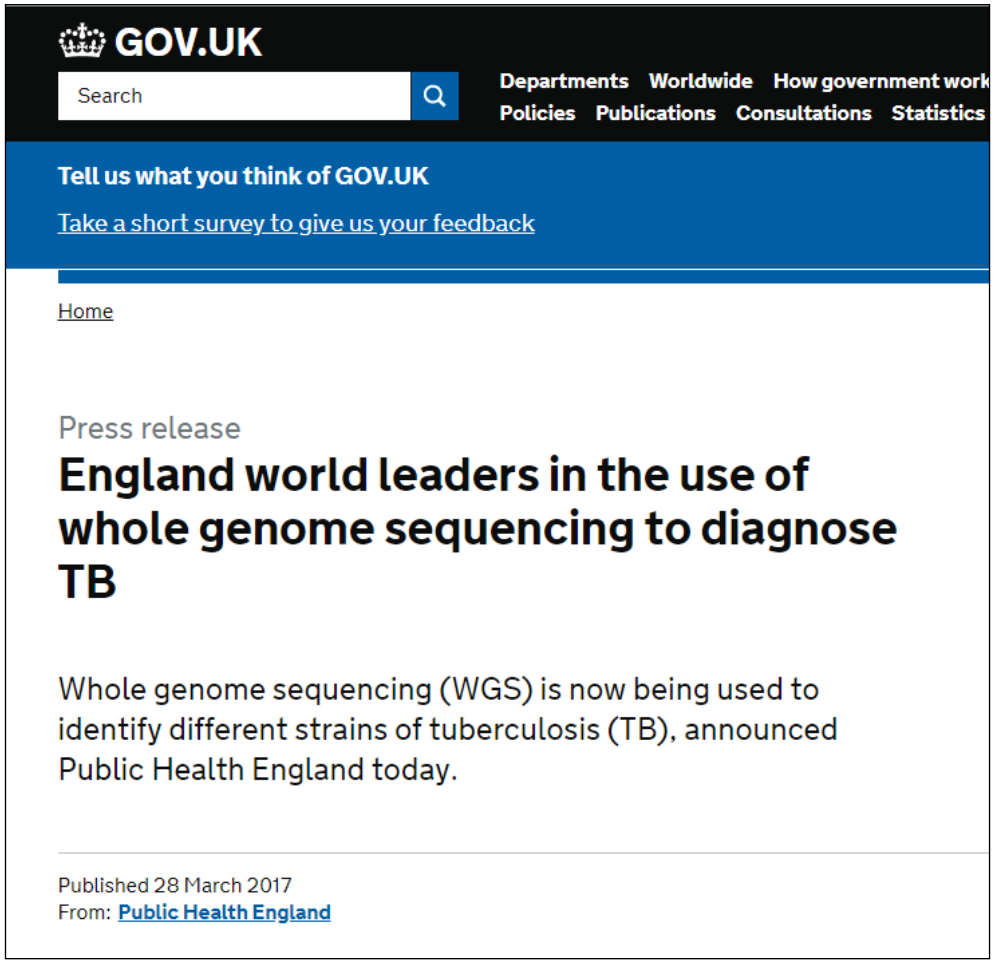

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Press release

England world leaders in the use of whole genome sequencing to diagnose TB

Whole genome sequencing (WGS) is now being used to identify different strains of tuberculosis (TB), announced Public Health England today.

Published 28 March 2017
From: Public Health England

- *"...This is the first time that WGS has been used as a diagnostic solution for managing a disease on this scale anywhere in the world..."*
- *"... Where previously it could take **up to a month** to confirm a diagnosis of TB, confirm the treatment choices and to detect spread between cases, this can now be done in **just over a week** by PHE's Birmingham laboratory..."*

https://www.gov.uk/government/news/england-world-leaders-in-the-use-of-whole-genome-sequencing-to-diagnose-tb

Example of pharmacogenomic testing: *DPYD*

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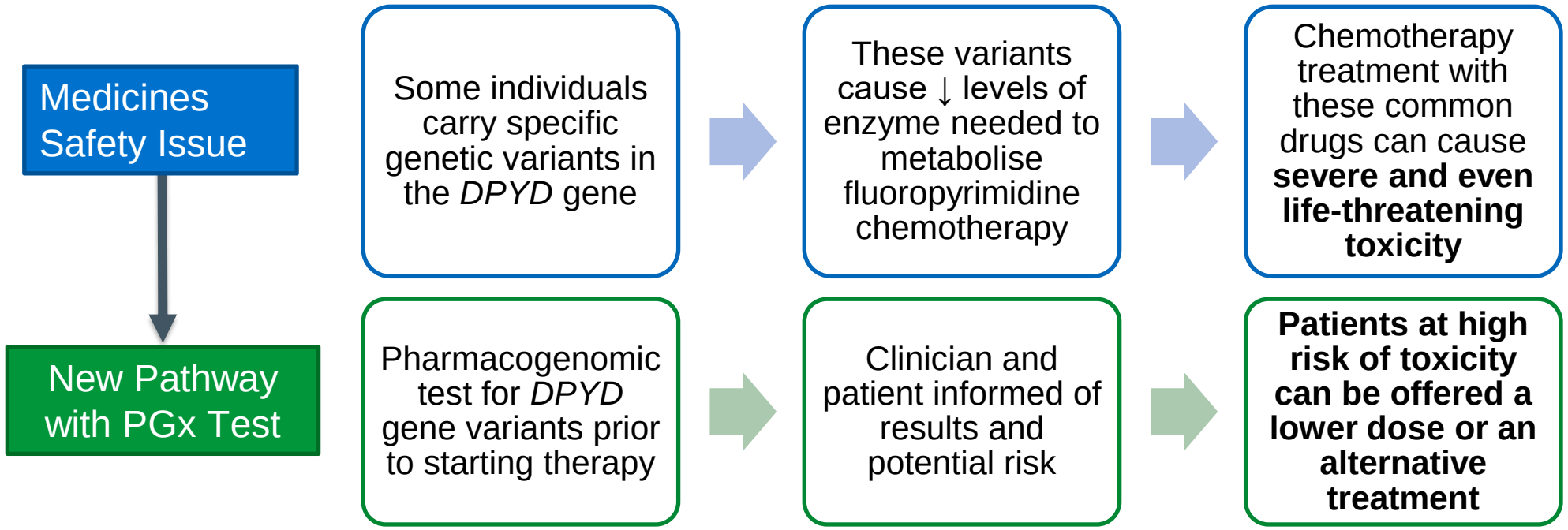
- *DPYD* pharmacogenomic test offered to all patients prior to starting fluoropyrimidine chemotherapy (5-fluorouracil, capecitabine) – 38k pts/yr



- Anticipated to ↓ severe toxicity (≥ grade 3), ↓ hospitalisation, ↓ deaths, ↓ use of rescue drug

With thanks to Rachel Palmer, SWGMSA https://www.england.nhs.uk/wp-content/uploads/2020/11/1869-dpyd-policy-statement.pdf

GOV.UK Topics

Home > Drug Safety Update

Flucytosine (Ancotil): new contraindication in patients with DPD deficiency

Flucytosine is a prodrug of 5-fluorouracil used to treat systemic yeast and fungal infections and can cause life-threatening and severe toxicity in patients with complete and partial dihydropyrimidine dehydrogenase (DPD) deficiency. Although pre-testing of DPD status before flucytosine treatment is not required, a new contraindication for patients with complete DPD deficiency has been introduced.

From: Medicines and Healthcare products Regulatory Agency

Published 22 October 2020

https://www.gov.uk/drug-safety-update/flucytosine-ancotil-new-contraindication-in-patients-with-dpd-deficiency

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Neonatal gentamicin hearing loss risk –
PALOH group (Manchester)

March 21, 2022

Rapid Point-of-Care Genotyping to Avoid Aminoglycoside-Induced Ototoxicity in Neonatal Intensive Care

John H. McDermott, MD, MRes[1,2]; Ajit Mahaveer, MD[3]; Rachel A. James, PhD[1]; et al

» Author Affiliations | Article Information

JAMA Pediatr. Published online March 21, 2022. doi:10.1001/jamapediatrics.2022.0187

https://jamanetwork.com/journals/jamapediatrics/fullarticle/2790066

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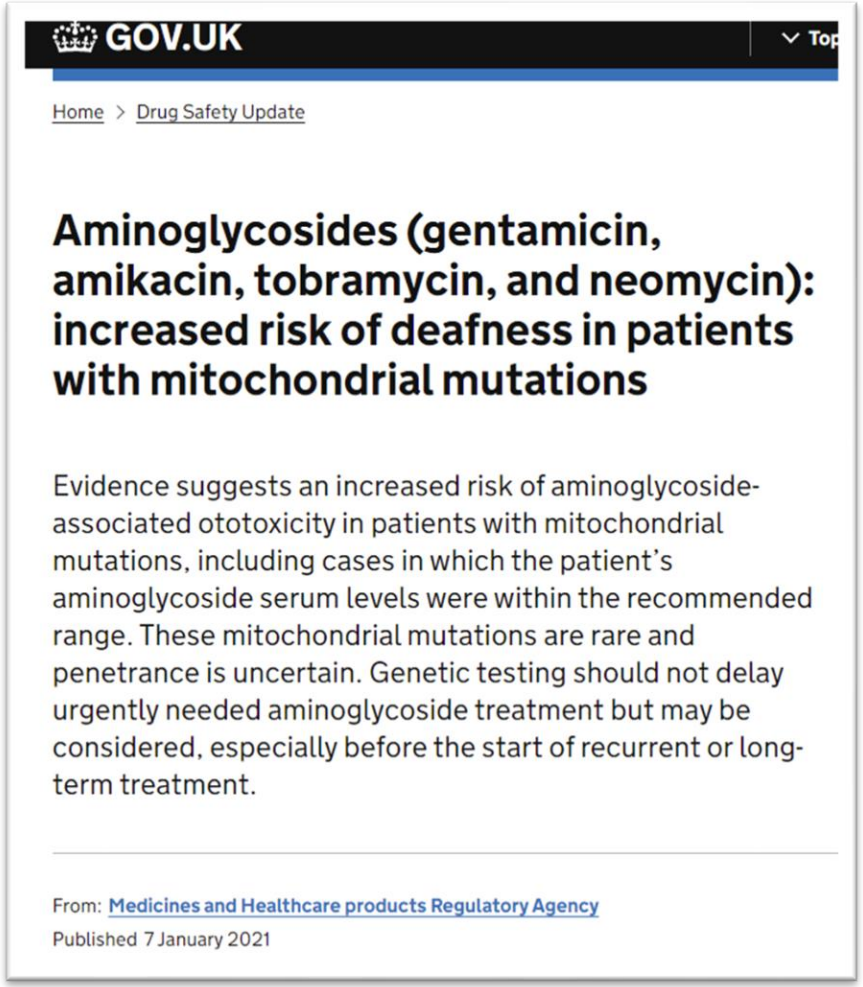
mtDNA mutation m.1555A>G and risk of hearing loss with aminoglycosides



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Home > Drug Safety Update

Aminoglycosides (gentamicin, amikacin, tobramycin, and neomycin): increased risk of deafness in patients with mitochondrial mutations

Evidence suggests an increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial mutations, including cases in which the patient's aminoglycoside serum levels were within the recommended range. These mitochondrial mutations are rare and penetrance is uncertain. Genetic testing should not delay urgently needed aminoglycoside treatment but may be considered, especially before the start of recurrent or long-term treatment.

From: Medicines and Healthcare products Regulatory Agency

Published 7 January 2021

- Epidemiological studies showing ↑risk of deafness in patients with m.1555A>G mutation given AG
- Prevalence approx. 1 in 500
- Some w Hx of maternal deafness
- No cases with topical AG (but potentially as same mech)

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Proposed mechanism of AG ototoxicity

- MT-RNR1 encodes 12S mitochondrial ribosomal subunit
- 12S is a homolog of prokaryotic 16S subunit (AG target)
- Certain variants in MT-RNR1 gene (e.g m.A1555G) make the 12S 'look like' the bacterial 16S
  - →AG binds 12S
  - →protein synthesis disrupted
  - →Cell death
- There are other variants that do this but rarer
  - May see expansion of the variants included in commissioned test

Krause et al 2016 DOI: 10.1101/cshperspect.a027029

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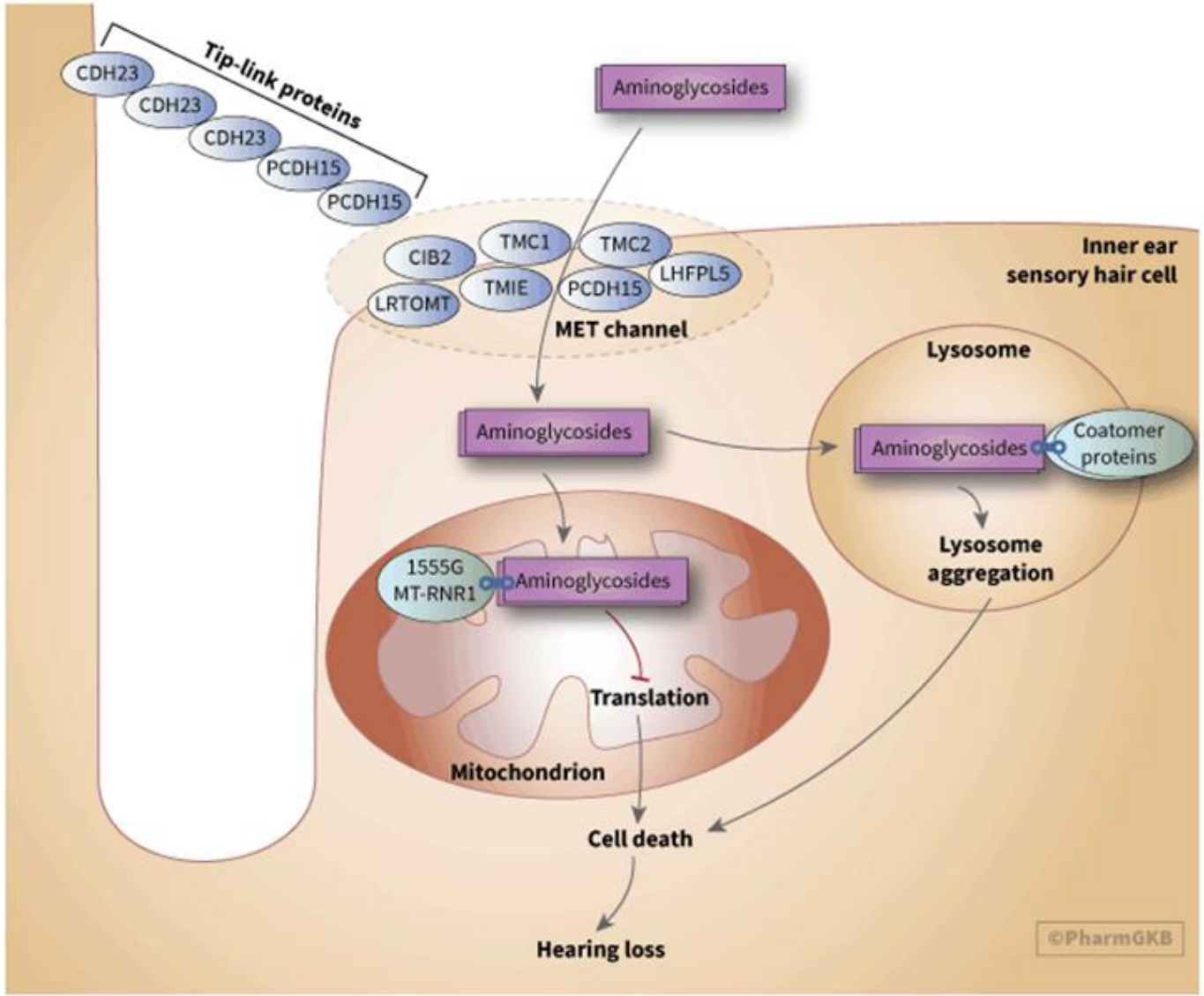
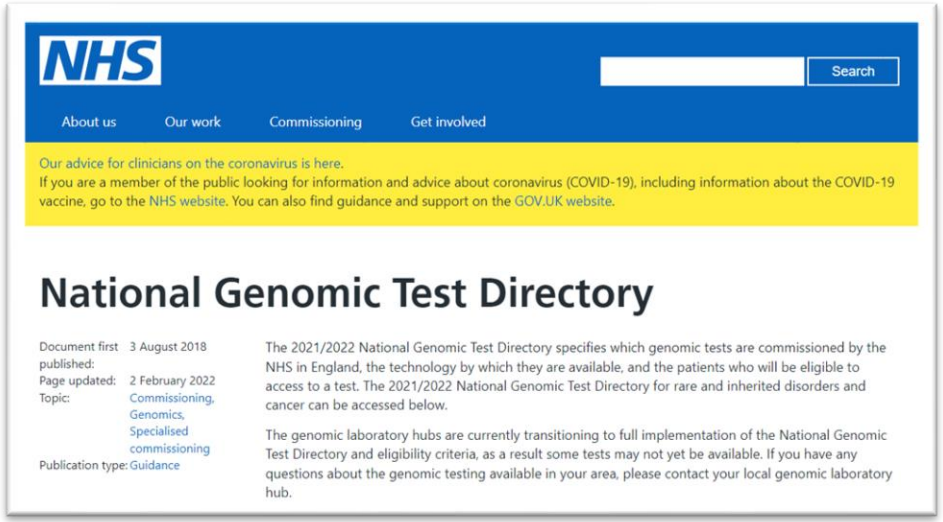


PharmGKb.org

Genomic test approval & commissioning

- NHSEI National Genomic Test Directory
  - Application process, test evaluation working groups
  - Ca/Rare Dis/?PGx



- **PGx: currently only DPYD, aminoglycoside (<u>not POC</u>)**
- Plus genomic tests historically commissioned by other routes e.g. abacavir, carbamazepine

https://www.england.nhs.uk/publication/national-genomic-test-directories/

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Part IX. Audiology

R65 Aminoglycoside exposure posing risk to hearing

Testing Criteria

Significant exposure to aminoglycosides posing risk of ototoxicity

This indication would be relevant to:

1. individuals with a predisposition to gram negative infections for example due to known respiratory

Significant exposure to aminoglycosides posing risk of ototoxicity

This indication would be relevant to:

1. individuals with a predisposition to gram negative infections for example due to known respiratory disease (e.g. bronchiectasis, cystic fibrosis) or due to structural or voiding genitourinary tract disorders, OR
2. individuals with hearing loss who have been exposed to aminoglycosides

- Other

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R65.1	MT-RNR1 1555A>G Targeted mutation testing	Singleton	Small variants	Single interval	MT-RNR1 1555A>G	Targeted mutation testing

https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-inherited-disease-eligibility-criteria-version-3.1-August-2022.pdf

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Where can I learn more?

Pharmacogenomics ‘Martindale’: PharmGKb.org

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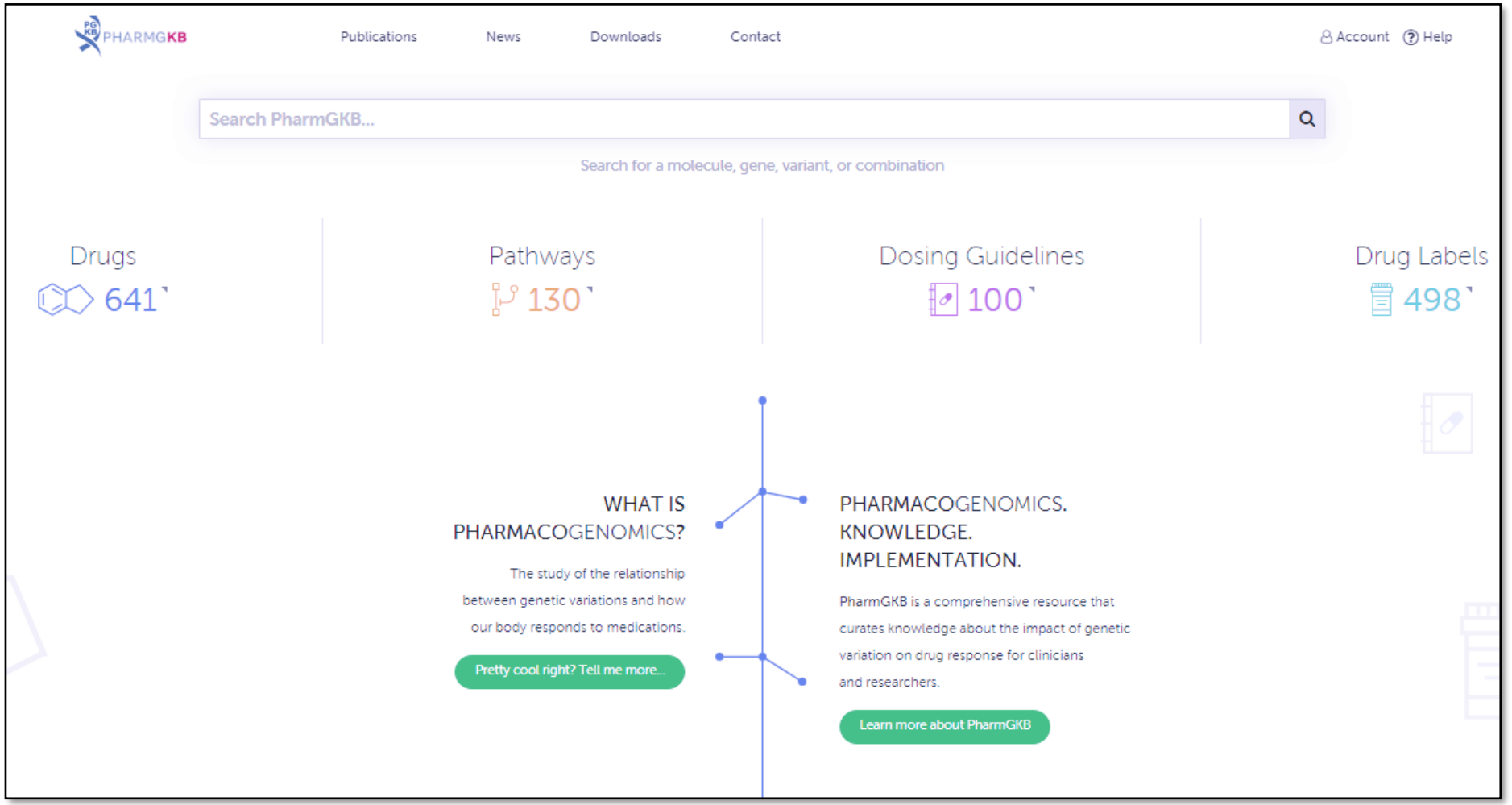

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https://cpicpgx.org/genes-drugs/

(N=448)
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CPIC® Guideline fo

Most recent guideline publication:

Clinical Pharmacogenetics Implementati
(April 2012)

Updates since publication:

May 2014: Guideline authors reviewed additiona
recommendations in the 2012 guideline; therefore
evidence table were updated (see below).

Tables and figure provided in the main m

Table 1. Assignment of likely HLA-B phenotypes based c
Table 2. Recommended therapeutic use of abacavir in r
Figure 1. Treatment algorithm for clinical use of abacavi

Supplement to: Clinical Pharmacogenetic
Abacavir Dosing (May 2014)

Tables and figures included in the supple

Supplemental Table S1. Frequencies of alleles in major
Supplemental Table S2. Detailed table with all referenc

Linking genetic variability to variability in drug-related phenotypes

There is substantial evidence linking the presence of the *HLA-B*57:01* genotype with phenotypic variability (see **Supplementary Table S3** online). The application of a grading system to the evidence linking genotypic variability to phenotypic variability indicates a high quality of evidence in the majority of cases (see **Supplementary Table S3**). The evidence described below and in **Supplementary Table S3** provides the basis for the recommendations in Figure 1 and Table 2.

In 2002, two independent research groups reported the initial association between *HLA-B*57:01* and abacavir HSR[24,25] using cohort and case–control designs. The association was replicated

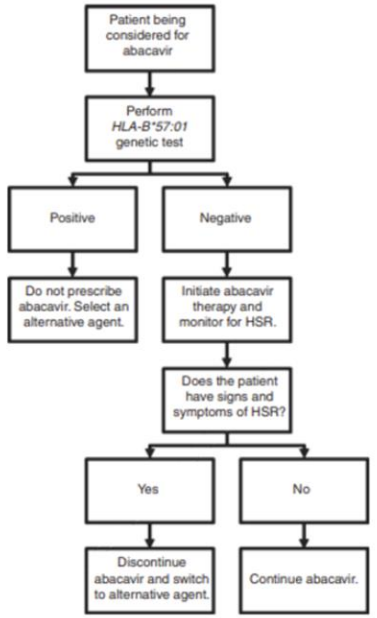

Figure 1 Treatment algorithm for clinical use of abacavir based on *HLA-B*57:01* genotype. HLA-B, human leukocyte antigen B; HSR, abacavir hypersensitivity reaction.

Moreover, the results of PREDICT-1, the first double-blind, prospective, randomized trial of a genetic test to reduce adverse drug events, showed that genetic prescreening for *HLA-B*57:01* resulted in no immunologically confirmed HSR events among *HLA-B*57:01*-negative patients in the genetic testing arm,[31] vs. a 2.7% incidence of immunologically confirmed HSR among 842 unscreened patients in the standard-of-care control arm. The results of PREDICT-1 and the existing body of evidence prompted the FDA to implement a black box warning in 2008 about the high risk of *HLA-B*57:01*-associated HSR. The FDA recommended that all patients be screened before being treated with abacavir (including those who had previously tolerated the drug and were being restarted on the therapy) and that abacavir not be initiated in carriers of *HLA-B*57:01*. Abacavir is one of a limited number of drugs for which the FDA has recommended genetic testing prior to use, and it remains one of the best examples to date of pharmacogenetics being integrated into routine medical practice.

Therapeutic recommendations

We agree with others[32–36] that *HLA-B*57:01* screening should be performed in all abacavir-naive individuals before initiation of abacavir-containing therapy (see Table 2); this is consistent with the recommendations of the FDA, the US Department of Health and Human Services, and the European Medicines Agency. In abacavir-naive individuals who are *HLA-B*57:01*-positive, abacavir is not recommended and should be considered only under exceptional circumstances when the potential benefit, based on resistance patterns and treatment history, outweighs the risk. *HLA-B*57:01* genotyping is widely available in the developed world and is considered the standard of care prior to initiating abacavir. Where *HLA-B*57:01* genotyping is not

Table 2 Recommended therapeutic use of abacavir in relation to *HLA-B* genotype

Genotype	Implications for phenotypic measures	Recommendations for abacavir	Classification of recommendations[a]
Noncarrier of *HLA-B*57:01*	Low or reduced risk of abacavir hypersensitivity	Use abacavir per standard dosing guidelines	Strong
Carrier of *HLA-B*57:01*	Significantly increased risk of abacavir hypersensitivity	Abacavir is not recommended	Strong

HLA-B, human leukocyte antigen B.
[a]Rating scheme described in **Supplementary Data** online.

Review

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Table 1. Genetic association with genes related to antibiotic drug pharmacokinetics.

Gene	Polymorphism	Antibiotic	Effect	Reference
SLC22A8	rs11568482	Cefotaxime (Cephalosporins)	Lower clearance	[33]
ABCC2 *ABCG2*	rs2273697 rs13120400	Ceftriaxone (Cephalosporins)	Higher drug concentration in CSF Reduction on drug CSF/plasma ratio	[41]
ABCC2	rs717620	Erythromycin (Macrolides)	Increase in drug metabolism	[52]
SLCO1B1	rs4149056		Reduction in drug metabolism	[53]
ABCB1	2677TT/3435TT	Azithromycin (Macrolides)	Lower C_{max} and higher T_{max}	[55]
UGT1A	rs8175347	Moxifloxacin (Fluoroquinolones)	Lower clearance	[83]
	rs3755319		Higher clearance	
ABCB1	rs2032582		Higher clearance	[83]
ABCB1	rs1045642		Higher T_{max}	[84]
SLCO1B1	rs4149015		Higher AUC_{0-24} and C_{max}	[85]
ABCB1	1236C > T rs1128503 2677G > T/A rs2032582 3435C > T rs1045642	Daptomycin	Higher AUC_{0-24}	[92]
ABCB1	rs1045642	Linezolid	Lower clearance	[97]

Table 2. MHC class I and II polymorphism associations with adverse reaction to antibiotics.

Gene	HLA Association	Antibiotics	Effect	Reference
HLA-DRB1	DRB1*15:01	Amoxicillin clavulanate (Penicillins)	DILI	[16–18]
HLA-DQB1	DQB1*06:14			[19]
HLA-DQB1	rs9274407			[20]
HLA-DRA	rs3135388			[20]
-	rs2523822			[20]
HLA-DRB1-HLA-DQB1	DRB1*15:01-DQB1*06:02			[8,16–18]
HLA-A	A*30:02			[21]
HLA-B	B*18:01			[21]
HLA-B	B*57:01	Flucloxacillin (Penicillins)		[24,26]
HLA-B	B*57:03			[26]
HLA-A	A*32:01	Vancomycin	DRESS	[88]
HLA-B	B*35:02	Minocycline	DILI	[99]
HLA-B	B*51:01	Clindamycin	Cutaneous reactior	

DILI: drug induced liver injury; DRESS: drug reaction with eosinophilia and systemic sy

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Royal College of Physicians | BRITISH PHARMACOLOGICAL SOCIETY

Personalised prescribing

Using pharmacogenomi
improve patient outcom

A report from the Royal College of Ph
British Pharmacological Society joint

https://www.rcp.ac.uk/projects/outputs/personalised-prescribing-using-pharmacogenomics-improve-patient-outcomes

- a pharmacogenomics consult service should be developed within each integrated care system (ICS) led by a multidisciplinary team comprising clinical pharmacologists, pharmacists and other interested specialists, taking into account guidelines and prescribing information. Given that most of the prescribing occurs in primary care, it is important that GPs and pharmacists are considered an essential component of this multidisciplinary pharmacogenomics service

Pharmacomicrobiomics!

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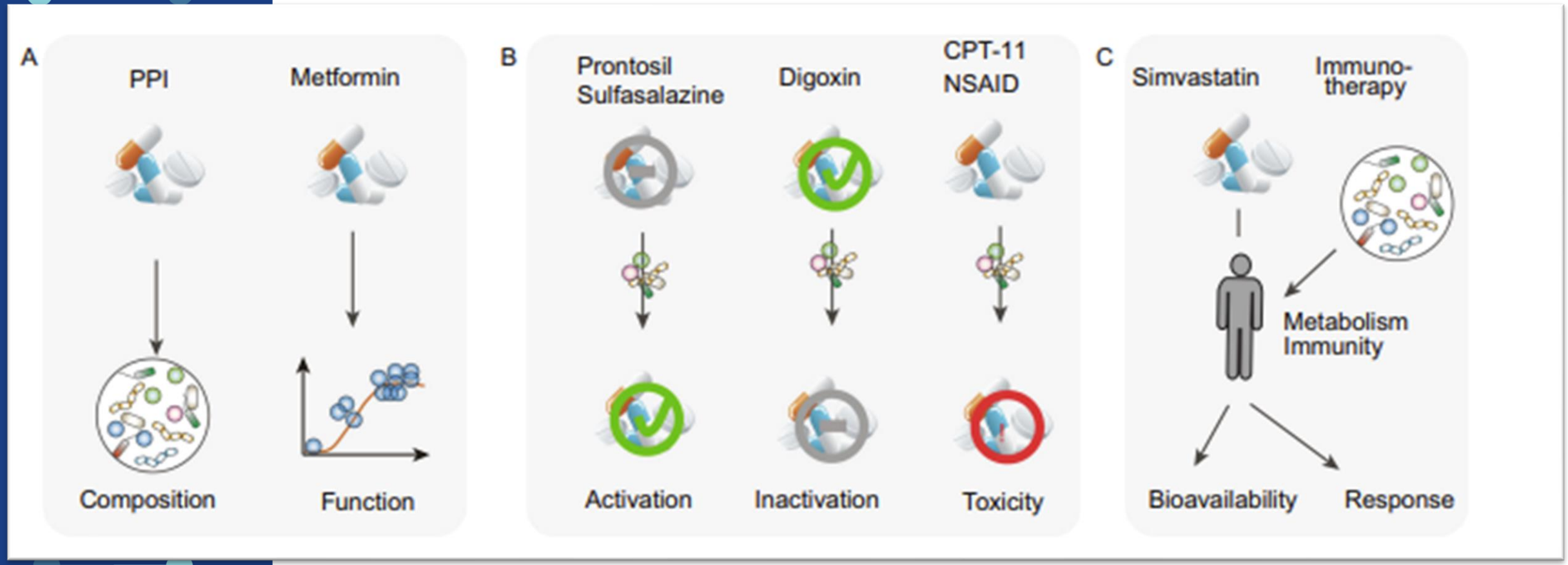
Sequencing to model the gut microbiome - Front. Genet., 23 June 2015 | https://doi.org/10.3389/fgene.2015.00219



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5960471/pdf/13238_2018_Article_547.pdf

Genomics education for pharmacy teams

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- HEE Genomics Education Programme
  - FREE online learning
  - Bite-size courses, modules, full funded MSc available for NHS staff
  - *https://www.genomicseducation.hee.nhs.uk/education/*
- CPPE Genomics module, FutureLearn MOOCs
- GeNotes – new!

- Talk to your GMSA pharmacist or national lead
- National Pharmacy Genomics Workforce Survey
  - All pharmacy staff, all sectors – being analysed

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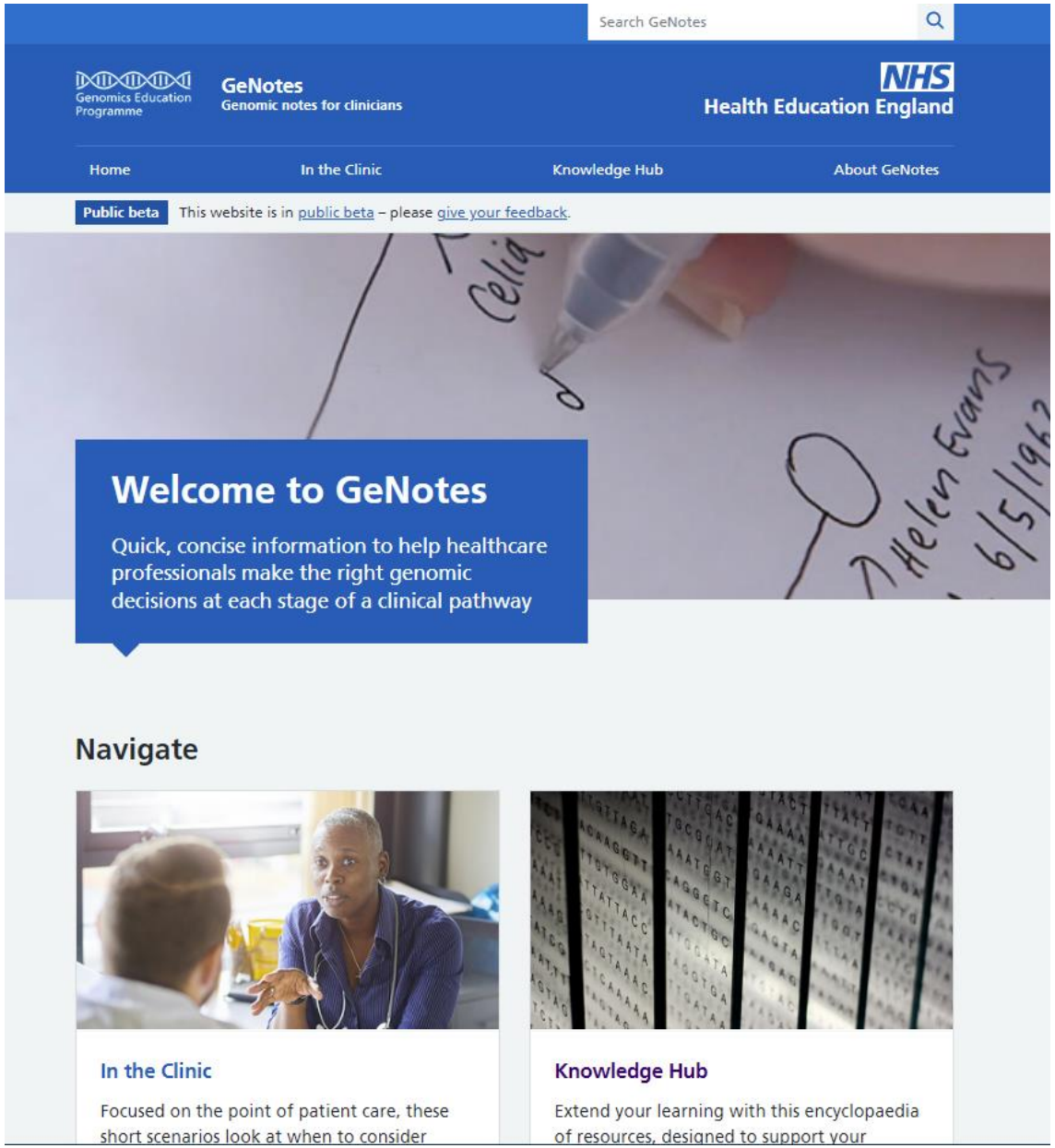

https://www.genomicseducation.hee.nhs.uk/genotes/

launches on 15 June with In the Clinic Oncology (and several other specialties soon to follow) and more than 60 Knowledge Hub resources.

Meet your genomics pharmacist!

(see also Sco, Wal & NI!)

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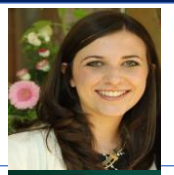
GMSA Region	Lead Genomics Pharmacist		Email
North East and Yorkshire	Emma Groves		Emma.Groves3@nhs.net
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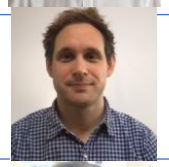
East	Paul Selby		Paul.Selby@addenbrookes.nhs.uk
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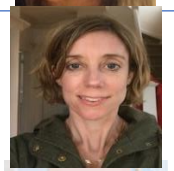
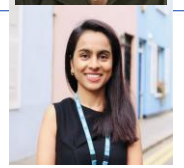
South West	Rachel Palmer		Rachel.Palmer6@nhs.net
North Thames	Dharmisha Chauhan		Dharmisha.Chauhan1@nhs.net
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Thank you

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